Office Action Summary	Application No.	Applicant(s)
	10/661,804	SCHULER ET AL.
	Examiner	Art Unit
	AMY JUEDES	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/28/11, 2/24/11*.	6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 2/24/11 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/24/11 has been entered.

Claim 12 has been cancelled.

Claims 25-29 and 33-34 have been amended.

Claims 35-36 have been added.

Claims 25-36 are pending and are under examination.

2. In view of Applicant's amendments and remarks, the previous grounds of rejection are withdrawn.

3. The following are new grounds of rejection.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-27 specify that the method further comprises "utilizing" immunoabsorption methods or a stimulating agent/antigen presenting cells. The methods do not specify how or when said immunoabsorption methods or stimulating agents/APCs are to be used. For example, are the immoabsorption methods or stimulating agents to be used in the isolating step or in the testing step recited in independent claim 34?

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-30 and 32-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Jonuleit et al., 2000 (of record).

Jonuleit et al. teach a method comprising isolating CD4+ T cells from the blood (i.e. "removing" the CD4+ T cells), stimulating the CD4+ T cells with immature dendritic cells, and isolating from said CD4+ T cells a population of CD4+CD25+ regulatory T cells. Jonuleit et al. further teach testing and confirming in said CD4+CD25+ T cells the constitutive expression of CTLA-4 (see page 1214, and 1216, in particular). Jonuleit et al. teach detecting CTLA-4 by contacting the regulatory T cells with an anti-CTLA-4 antibody and detecting binding of the antibody to the cells (see page 1214, in particular). Jonuleit et al. teach testing the CD4+CD25+ regulatory T cells and determining that they have a cytokine profile of predominate secretion of IL-10 and only low levels of IL-2, IL-4, and IFN-gamma (see page 1216, in particular). Jonuleit et al. teach isolating the CD4+ T cells by immunoadsorption techniques (see page 1214, in particular). The method of isolating the CD4+CD25+ from the CD4+ T cells involves stimulating with immature dendritic cells (i.e. the method utilizes antigen presenting cell). Jonuleit et al. teach that the CD4+CD25+ suppress proliferation and activation of CD4+ T cells in co-culture in cell contact dependent and cytokine independent manner (see page 1216-1217, in particular).

Thus, the reference clearly anticipates the invention.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-30 and 32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taams et al., 2000, in view of Jonuleit et al., 2000, and Read et al., 2000 (all of record).

Taams et al. teach a method comprising depleting/isolating CD4+CD25+ regulatory T cells from an isolated population of human peripheral CD4+ T cells. Taams et al. teach testing the CD4+CD25+ T cells for expression of CTLA-4, and teach that the isolated CD4+CD25+ T cells express CTLA-4. Taams et al. teach testing the CD4+CD25+ T cells for being in an anergic state. Taams et al. teach testing the CD4+CD25+ T cells for their ability to inhibit proliferation of CD4+ T cells in a co-culture, and teach that that said inhibition is contact-dependent and cytokine independent. Taams et al. teach testing the CD4+CD25+ regulatory T cells for suppressive function in the presence of APC (i.e. the method utilizes antigen presenting cells).

Tams et al. do not teach isolating the CD4+ T cells from the blood, nor do they characterize the expression of CTLA-4 as "constitutive".

Read et al. teach that the expression of CTLA-4 on CD4+CD25+ T cells isolated directly ex-vivo is considered to be "constitutive" expression (see page 299, in particular).

Jonuleit et al. teach that peripheral CD4+ T cells can be readily isolated from the peripheral blood of human subjects for the characterization of CD4+CD25+ regulatory T cells. Jonuleit et al. teach that human and mouse CD4+CD25+ regulatory T cells constitutively express CTLA-4 (see page 1214 and 1216, in particular). Jonuleit et al. teach detecting CTLA-4 by contacting the regulatory T cells with an anti-CTLA-4 antibody and detecting binding of the antibody to the cells (see page 1214, in particular). Jonuleit et al. teach testing the CD4+CD25+ regulatory T cells and determining that they have a cytokine profile of predominate secretion of IL-10 and only low levels of IL-2, IL-4, and IFN-gamma (see page 1216, in particular). Jonuleit et al. teach isolating the CD4+ T cells by immunoabsorption techniques (see page 1214, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine that the CTLA-4 expression by the ex-vivo isolated CD4+CD25+ regulatory T cells of Taams et al., is "constitutive" since Read et al. teach that expression of CTLA-4 by CD4+CD25+ T cells isolated directly ex-vivo is considered to be "constitutive" expression. Moreover, Jonuleit et al. further teach that CD4+CD25+ regulatory T cells in humans and mice "constitutively" express CTLA-4. Furthermore, it would have been obvious to obtain the CD4+ population of human peripheral T cells from the peripheral blood, since Jonuleit et al. teach that teach that human peripheral CD4+ T cells can be readily isolated from peripheral blood by immunoabsorption techniques. Additionally, it would have been obvious to further test the regulatory T cells of Taams et al., for cytokine expression, since Jonuleit et al. teach that human CD4+CD25+ regulatory T cells have a cytokine profile of predominate secretion of IL-10 and only low levels of IL-2, IL-4, and IFN-gamma. Furthermore, it would have been routine and well within the purview of the ordinary artisan to test for CTLA-4 expression using a CLTA-4 antibody, as taught by Read et al. and Jonuleit et al.

7. Claim 25-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jonuleit et al., 2000, in view of Stout et al., 1993 (of record).

The teachings of Jonuleit et al. are discussed above.

Jonuleit et al. do not teach testing the regulatory properties of CD4+CD25+ regulatory T cells using CD4+CD25+ T cells that have been fixed.

Stout et al. teach that T cells effector functions that are contact dependent, but cytokine independent, can be mediated even when the T cells are fixed after activation.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Stout et al. to the methods of testing the regulatory function of the CD4+CD25+ T cells of Jonuleit et al.. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, since Jonuleit et al. teach that activated CD4+CD25+ regulatory T cells function via a cytokine independent, contact dependent mechanism, and Stout et al. teach that contact dependent, cytokine independent T cell functions can be performed even after fixation of the activated T cells.

8. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Taams et al., 2000, Jonuleit et al., 2000, and Read et al., 2000, as applied to claims 25-30 and 32-36 above, and further in view of Stout et al., 1993 (of record).

The combined teachings of Taams et al., Jonuleit et al., and Read et al. are discussed above.

They do not teach testing the regulatory properties of CD4+CD25+ regulatory T cells using CD4+CD25+ T cells that have been fixed.

Stout et al. teach that T cells effector functions that are contact dependent, but cytokine independent, can be mediated even when the T cells are fixed after activation.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Stout et al. to the methods of testing regulatory function of the CD4+CD25+ T cells made obvious by Taams et al., Jonuleit et al, and Read et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, since Taams et al. teach that activated CD4+CD25+ regulatory T cells function via a cytokine independent, contact dependent

mechanism, and Stout et al. teach that contact dependent, cytokine independent T cell functions can be performed even after fixation of the activated T cells.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 8am to 4:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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